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Comprehensive embryo testing. Experts' opinions regarding future directions: an expert panel study on comprehensive embryo testing

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STUDY QUESTION: What do scientists in the field of preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) consider to be the future direction of comprehensive embryo testing?

SUMMARY ANSWER: Although there are many biological and technical limitations, as well as uncertainties regarding the meaning of genetic variation, comprehensive embryo testing will impact the IVF/PGD practice and a timely ethical reflection is needed.

WHAT IS KNOWN ALREADY: Comprehensive testing using microarrays is currently being introduced in the context of PGD and PGS, and it is to be expected that whole-genome sequencing will also follow. Current ethical and empirical sociological research on embryo testing focuses on PGD as it is practiced now. However, empirical research and systematic reflection regarding the impact of comprehensive techniques for embryo testing is missing.

STUDY DESIGN, SIZE AND DURATION: In order to understand the potential of this technology and to be able to adequately foresee its implications, we held an expert panel with seven pioneers in PGD.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We conducted an expert panel in October 2011 with seven PGD pioneers from Belgium, The Netherlands, Germany and the UK.

MAIN RESULTS AND THE ROLE OF CHANCE: Participants expected the use of comprehensive techniques in the context of PGD. However, the introduction of these techniques in embryo testing requires timely ethical reflection as it involves a shift from choosing an embryo without a particular genetic disease (i.e. PGD) or most likely to result in a successful pregnancy (i.e. PGS) to choosing the best embryo based on a much wider set of criteria. Such ethical reflection should take account of current technical and biological limitations and also of current uncertainties with regard to the meaning of genetic variance. However, ethicists should also not be afraid to look into the future. There was a general agreement that embryo testing will be increasingly preceded by comprehensive preconception screening, thus enabling smart combinations of genetic testing.

LIMITATIONS, REASONS FOR CAUTION: The group was composed of seven participants from four Western Europe countries. As willingness to participate in this study may be connected with expectations regarding the pace and direction of future developments, selection bias cannot be excluded.

WIDER IMPLICATIONS OF THE FINDINGS: The introduction of comprehensive screening techniques in embryo testing calls for further ethical reflection that is grounded in empirical work. Specifically, there is a need for studies querying the opinions of infertile couples undergoing IVF/PGS regarding the desirability of embryo screening beyond aneuploidy.

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Introduction

Genetic testing of biopsied cells from *in vitro* embryos is currently done for two different reasons in two different contexts. The first one is when prospective parents have an increased (recurrence) risk of conceiving a child with a genetic (in most cases Mendelian or chromosomal) disorder. This is called preimplantation genetic diagnosis (PGD). In many cases, this regards fertile couples who want to avoid transmitting the genetic condition, but prefer not (again) to try the route of prenatal diagnosis and a possible termination of pregnancy. As long as PGD is used for highly penetrant mutations and serious disorders, it is a relatively uncontroversial option, although the status of the preimplantation embryo remains a topic of controversy. Preimplantation genetic screening (PGS), secondly, is the routine testing of embryos resulting from IVF treatment. Currently, such screening is limited to testing for aneuploidy. A set of selected (or all) chromosomes are counted, to check for monosomy (the lack of one chromosome of the normal complement), trisomy, tetrasomy or pentasomy (the presence of three, four or five copies of a given chromosome), with the assumption that transferring an euploid embryo, which has only two copies of a given chromosome, will enhance the chance of a successful pregnancy (Fragouli and Wells, 2012). Worldwide, many centres have started offering PGS for patients with advanced maternal age, recurrent implantation failure or recurrent pregnancy loss, as those groups would theoretically benefit most from such screening. However, the American Society of Reproductive Medicine (ASRM), the British Fertility Society and the European Society of Human Reproduction and Embryology (ESHRE) have concluded that PGS using fluorescent *in situ* hybridization (FISH) does not, at the moment, improve the live birth rates in those patient groups (Mastenbroek *et al*., 2007; Anderson and Pickering, 2008; Harper and Sengupta, 2011). One factor responsible for this lack of success is the phenomenon of mosaicism: the fact that the cell(s) taken from the embryo may not be representative of the rest of the embryo, especially when the embryo biopsy is done at the cleavage stage (Day 3). As a result, a fraction of embryos that would be able to develop into healthy fetuses are excluded from transfer. A second assumption is that FISH, which was thus far the main method used, looks at less than half of the chromosomes at the same time, thereby possibly missing important information from the other chromosomes. Moreover, the presence, absence or the interpretation of FISH signals is not always straightforward and may lead to misdiagnosis. Thirdly, embryo biopsy, especially at the cleavage stage, may negatively influence an embryo's viability. Microarrays, such as array-CGH (comparative genomic hybridization) and SNP array, allow for the screening of all chromosomes simultaneously, removing the second limitation. They also allow for the detection of submicroscopic chromosomal abnormalities such as large insertions or deletions. This technique also seems more reliable and may result in less misdiagnosis. If the polar body (Day 1) or trophectoderm cells (Day 5) are used, this is deemed to be less invasive for the embryo. Some studies have shown a positive effect on the chance of a successful pregnancy with the use of microarray technology for such 'comprehensive' chromosome screening (Forman *et al*., 2012; Scott *et al*., 2012; Treff *et al*., 2012; Yang *et al*., 2012). More randomized controlled trials are underway to test the efficiency of PGS by means of microarray analysis at the zygote stage by looking at polar bodies (Harper *et al*., 2008, 2010; Geraedts *et al*., 2010). Besides the already available microarray technology, it is expected that whole-genome sequencing of single cells will eventually be clinically applicable in the context of embryo testing as well (Baslan *et al*., 2012).

A considerable number of empirical sociological and psychological studies have been published reporting qualitative and quantitative data about traditional PGD (Miedzybrodzka *et al*., 1993; Palomba *et al*., 1994; Snowdon and Green, 1997; Lavery *et al*., 2002; Roberts and Franklin, 2004; Zeiler, 2004; Ehrich *et al*., 2006, 2007; Williams *et al*., 2007; Ehrich and Williams, 2010). These studies typically aim to describe the dynamics of PGD as it is currently practiced, targeting specific diseases, and to provide insight into the experiences of practitioners and patients.

Preimplantation genetic testing has also been widely discussed in the ethics literature. Issues covered include the status of the human embryo, the principle of respect for reproductive autonomy, the impact of reproductive testing and selection on the rights of the disabled in society, a supposed duty to select the best embryo and fears regarding a slippery slope toward creating 'designer children' (Robertson, 2003; Savulescu and Kahane, 2009; Wilkinson, 2010).

We are now on the verge of the era of comprehensive genetic tests, such as microarray analysis and whole-genome sequencing. This may revolutionize our knowledge of embryos' genotypes and substantially increase the options for informed selection. Moreover, progress on the genetic level has gone hand in hand with progress in IVF-related techniques such as vitrification and *in vitro* maturation of oocytes (Kuwayama *et al*., 2005; Zheng *et al*., 2005; Wang *et al*., 2011). Embryo freezing may remove current limitations on time schedules needed for diagnostic tests, whereas *in vitro* maturation may increase the number of oocytes and, as a consequence, embryos to select from. The implications of this evolution call for a timely ethical reflection, which should be embedded in scientific reality but not afraid to assess potential future directions as well (De Wert, 2009). To understand the dynamics of comprehensive embryo testing and to assess the scope and content of ethical reflection on this topic, we queried the opinions of PGD pioneers in an expert panel.

Materials and Methods

In order to arrive at an exploration of possible ethical questions informed by an inside assessment of the pace and direction of

technological developments in the field of genetic testing and artificial reproductive technologies (ART), we invited a group of pioneers of embryo testing for an expert panel at Maastricht University. The meeting was held in the context of a campus course on comprehensive embryo testing organized by the special Interest Groups 'Reproductive Genetics' and 'Ethics & Law' of ESHRE. Participants in the expert panel were seven scientific experts with many years of experience in PGD. [The participants were Edith Coonen (Maastricht University), Christine De Die-Smulders (Maastricht University), Joep Geraedts (Maastricht University), Alan Handyside (The Bridge Fertility Centre, London), Joyce Harper (University College London), Udo Koehler (Medizinisch Genetisches Zentrum, Munich), Karen Sermon (Free University of Brussels) and Evelyne Vanneste (Catholic University of Louvain).]

A topic guide was developed by K.H., W.D. and G.W., describing four different possibilities of the future direction of embryo testing. Participants were asked to reflect on these possibilities and give their technical and ethical opinions. First, we presented the possibility that aneuploidy screening was added to PGD for specific disorders. Secondly, we queried the participants about the possibility to test for many Mendelian conditions simultaneously, both in the context of PGD and PGS. Thirdly, the possibility of also screening embryos for complex disorders was discussed. To conclude, the more futuristic scenario of testing for non-health-related traits was presented to the participants. G.W. and W.D. were moderators; K.H. was an observer. The meeting was taped and later transcribed and analyzed by K.H., G.W., J.G. and W.D., using NVIVO9 to extract the main themes. In this report, we shall describe the result of this analysis and the consequences for the ethical debate on the issue. In order to avoid easy recognizability of individual contributions, all participants are referred to as 'she' and 'her'. Quotes are included quasi-literally, but we have inserted clarifications in square brackets where necessary and have adapted some words to increase understandability.

Results and Discussion

Possibilities and limitations of embryo testing

Increasing the resolution of genetic embryo testing is a recent development, and therefore still subject to uncertainties regarding its future direction, for example, regarding the applicability of whole-genome sequencing. At present, there are many aspects that limit the development of its full potential. Our participants mentioned three types of limitations: technical limitations related to the state of the art of the technology itself, biological limitations and limitations related to the current lack of knowledge regarding the meaning of genetic variance. Technical limitations were related to current testing techniques, specifically the difficulty of single-cell whole-genome sequencing and the amplification of DNA. Also, the limited number of embryos resulting from an IVF cycle, which is a biological limitation, severely limits the range of possible applications of embryo testing today. However, participants were also convinced that such technical limitations will most likely be overcome in the not too distant future.

> . . . , but before that nobody could foresee that PCR would be that successful for a number of applications.

In this quote, the participant asserts her belief that even technical limitations that seemed insurmountable in the past have been overcome and, consequently, the same will be true for current and future technical limitations.

Apart from technical, and surmountable, limitations, participants also stressed the importance of acknowledging biological limitations, which may be more difficult, if not impossible, to overcome, as is clear from the following quote:

> But who knows in the future, yes we may have better whole genome amplification but we are still limited by the biology.

One such limitation participants repeatedly quoted is the fact that in a woman of advanced maternal age, the number of oocytes without chromosomal abnormalities is limited if not zero. Another biological limitation is that embryo selection is limited by the fact that, apart from *de novo* mutations, all genetic variation is inherited from either parent. These limitations may effectively tighten the scope of selection, or make the technique unreliable altogether.

However, there was firm belief among some participants that comprehensive screening of embryos will ultimately be possible and will be practiced, and that this development has already taken a start now:

> . . . as far as I am concerned, GATTACA is here. We could do this at a basic level now, we could do a genome scan of the parents and then decide what we want to do with the embryo. Right now, we are already doing a genome scan of the embryo and selecting the fittest embryo.

The participant refers here to the movie GATTACA, a dystopic tale depicting a future where many people are selected after genetic analysis and profiling of embryos resulting from ART.

Finally, participants stated that the techniques to detect genetic variation evolve far more rapidly than knowledge about the interpretation of genetic variants. They disagreed with the view that the more comprehensively embryos are tested, the more transparent they will become, as is clear from the following quote:

> The possibility of fully understanding the embryo are separate from the possibility of comprehensively screening and testing the embryo on each level I think.

The term comprehensive is therefore first and foremost applicable to the technique of screening and sequencing rather than to the actual interpretation. This may directly lead to the concern that, as long as knowledge is lagging behind, couples seeking PGS or PGD may be presented with genetic information of unknown significance and may take probabilities for certainties. Obviously, this has major implications for genetic counselling, as is clear from the following quote:

> I mean the fact that you generate data that you don't know how to communicate to the couple. . . . Even we ourselves do not understand the data we are generating. I think that generates ethical dilemmas that we should discuss.

In this quote, the participant explicitly states that this asymmetry between the information these techniques yield and the knowledge available to fully understand the test results raises important ethical issues that need to be well thought through. It is a call to ground ethical reflection firmly in realistic dilemmas that are already foreseeable.

However, participants also stressed the need for ethicists to look beyond technical, biological and informational limitations and consider a future where these limitations are overcome:

> But I think ethicists should look forward and should try to foresee future problems. What if we look at the whole genome and if we look at things like CNVs [Copy Number Variants] and cancers, cancer genes or high risk genes for for example high blood pressure or that stuff. That's I think the important discussion.

The abundance of information that may be yielded by such comprehensive tests, together with the gaps in the current knowledge about genetic variation and the fact that many genetic mutations yield probabilistic information, raised questions amongst our participants about how to communicate this information to the couple and how to facilitate decision-making. In the study of PGD staff by Williams *et al*., it is stated that PGD staff would find it difficult to argue with couples requesting PGD for genetic risk factors, such as BRCA mutations, as such couples already have experience with these conditions in their families (Williams *et al*., 2007). If such information comes as an add-on to the original clinical question, this experience is absent, which will potentially complicate decision-making. A further issue in this regard concerns the challenge of presenting the information on what choices between embryos have to be made in a way that would allow meaningful informed consent. Also, the possibility that each embryo may have a number of genetic abnormalities, either related to degrees of viability in the womb or to health, be it congenital or later in life, may lead to the fact that difficult or even impossible trade-offs will have to be made by the couple or by the professionals involved (Health Council of the Netherlands, 2010). The ideal standard of non-directive genetic counseling states that professionals should provide information and support that enables their clients to make their own well-informed decisions. This is based on the moral principle of respect for autonomy. However, authors have questioned whether such autonomous choice is actually possible or even desirable in the context of PGD (Williams *et al*., 2002). Roberts and Franklin have found in their ethnographic study of PGD that couples are well aware of the fact that their choices required careful thought and consideration about the implications and issues at stake (Roberts and Franklin, 2004; Franklin and Roberts, 2006). But the finding that most, if not all, couples undergoing traditional PGD do in fact make well-considered decisions cannot automatically be extended to the context of comprehensive genetic screening in the context of PGS. Here, there is potentially an explosion of choices and technological possibilities that couples may believe are necessary to explore or feel they cannot refuse. How grounded the fear that this may compromise their decision-making capacity is can only be answered by further research into the experiences of couples opting for IVF/PGS.

Broadening the scope: from single defects to genetic health profiles

The participants regarded 'testing for a specific disease combined with screening for chromosomal abnormalities' as a potentially valuable add-on to traditional PGD for particular genetic disorders. Such screening may facilitate the selection of an embryo that is both without the genetic disorder that was the indication for PGD and that is likely to implant as it has no serious chromosomal disorder. Moreover, as comprehensive chromosome screening can reveal trisomy-21 or other viable chromosomal abnormalities, including submicroscopic chromosomal abnormalities, such screening also implies screening for embryos with serious but viable conditions:

> So it is all the way from gross genetic defects that simply affect the embryo viability through to milder imbalances that give rise to potentially affected children.

This means that not only do these techniques allow for the selection of an embryo most likely to lead to a succesful pregnancy, but also to select against embryos likely to develop into a child with a chromosomal defect with multiple congenital anomalies and mental retardation.

Adding comprehensive chromosome screening to a PGD procedure aimed at avoiding a specific genetic disease may increase the chance that an embryo is chosen that will likely implant and unaffected by the condition in question and unrelated chromosomal abnormalities. Ehrich and Williams have presented the idea that the practice of selecting embryos in the context of traditional PGD, focusing on single disorders, is subject to a 'double imperative': PGD automatically involves IVF, a practice which is traditionally aimed at producing viable pregnancies, hopefully leading to the birth of a 'healthy' child. In view of the combined aims of IVF and PGD, therefore, embryos must be judged viable by embryologists and unaffected by geneticists (Ehrich and Williams, 2010).

The fact that there is this double imperative in the context of traditional PGD may, we think, explain why adding comprehensive chromosome screening to PGD seemed logical to our participants, as this would allow selecting against non-viable embryos and affected embryos alike. Conversely, if the original aim of PGS is to improve the chances that IVF will help the couple to have a baby, adding screening for common genetic mutations to PGS would make it possible for the professional to help them to have a *healthy* baby, thus answering to the same double imperative also when testing is done in the context of traditional IVF. However, it is relatively straightforward that a couple opting for PGD has hopes for a successful pregnancy, but an infertile couple hoping for a successful pregnancy may not automatically desire genetic testing for a range of conditions, a distinction worth reflecting on before introducing these tests in the clinic.

It was stated by our participants that the use of higher resolution techniques such as SNP arrays and eventually whole-genome sequencing allow for 'testing for a specific disease and other gene defects, including copy number variants (CNVs) and chromosomal aberrations simultaneously'. Participants mentioned the identification of genes coding for infertility as a first application that may be especially useful for the group of subfertile patients. One participant saw great potential and public health gain in the growing knowledge about the relation between CNVs and mental retardation:

> So the same copy number variants are now being associated with mental retardation and people have argued that every pregnancy should be screened for CNVs. Because the impact on the health system of avoiding these genetic causes of mental retardation and so on would be quite considerable.

Here, she describes how discussions about the increasingly higher resolution of the technology in prenatal testing are already ongoing, and that a reflection on testing embryos for CNVs as well is needed. Also the 'inclusion of testing for risk factors and complex

diseases' was considered by our participants. One of the main drawbacks with this inclusion they saw is the current lack of knowledge about the meaning of genetic variation that was discussed in the previous section. Another drawback is the fact that, if all genes and conditions were to be considered, no unaffected embryos would be left to transfer:

> I think we are here on the edge now, because everyone of us is abnormal. And if we then screen at a very high level, we cannot choose the normal embryo, because every embryo will become abnormal. We have to choose a combination of abnormalities to give to the parents, and [give back] the most normal.

Indeed, it may no longer be possible to pick an unaffected embryo. Instead, rather than a 'healthy' embryo, the embryo with the best health profile will be transferred.

So far, broadening the scope of PGD has been studied in the empirical literature in the context of broadening the number of conditions for which targeted PGD would be indicated. A study by Williams *et al.* describes opinions of staff of PGD clinics regarding PGD for late onset or low penetrance diseases. They found that staff had concerns about widening the criteria for doing PGD, but also thought it difficult to argue with couples who had first-hand experience with the condition in question (Williams *et al.*, 2007). However, if such conditions are detected as part of comprehensive PGS or PGD, rather than being the initial reason why the procedure is requested, some of the barriers may be lifted. Indeed, the discussion about allowing targeted PGD for additional conditions is partly one about the proportionality of the procedure. As PGD involves IVF, the benefits of allowing PGD for less serious, late onset or low penetrance diseases may not weigh up against the burdens, risks and material or immaterial costs of the procedure. However, if such information comes for free along with the information actually sought for, this barrier is already lifted and expansion of the scope of testing may be more acceptable for some people.

Broadening the scope: from health-related to non-health-related characteristics

Evolving genetic knowledge and comprehensive testing techniques may also lay bare the pathway toward testing for non-medical traits. This possibility was something some of the participants were anxious about. In this respect, sex selection was thought to be the 'first snowflake' on the route to prospective parents wanting to select an embryo with many other non-health-related characteristics. As discussed in the previous section, one participant explicitly mentioned the 1997 movie GATTACA, depicting a future society where most conceptions involve screening embryos and selecting the embryo with the best potential of developing into a child that will flourish in society. It was clearly pointed out that the techniques in that movie are not applied as of yet, but they might be sooner or later. One participant particularly was convinced that couples would be interested in this type of selection, should selection based on such traits become technically possible:

> If you look at how some parents force their children to go to music schools without having a perfect pitch, and to do well in sports and to have classes after. . . . Everybody wants the perfect child, and there are very few parents that can accept defaults or flaws in their children. (. . .) I think many parents will accept the notion—whether that is right or wrong—, but they will accept the step to going to select traits in their children or in the embryos or whatever.

This participant saw the desire to genetically select the 'best performing' child as a logical next step in a society where parents invest heavily in their children. Interestingly, she mentions the fact that parents often also force children to perform, be it in sports or in music. Selecting children with desirable traits is considered analogous to other types of parental pressure.

The qualitative interview study by Roberts and Franklin describes how couples undertaking traditional PGD grounded their wish to undertake PGD in the context of a parental duty to avoid grave suffering and premature death and clearly resented any association with the concept of a 'designer baby' (Roberts and Franklin, 2004). However, as genetic knowledge progresses even further, embryos could perhaps also be selected for non-medical characteristics, such as intelligence. Although knowledge about the genetics of such complex traits is still limited today, studies have already demonstrated the genetic basis of traits such as absolute pitch and height (Weedon *et al.*, 2007; Theusch *et al.*, 2009; Lango Allen *et al.*, 2010), traits which may be of potential interest to future parents. This would ultimately mean that one could not only select for a healthy child or a child with the best health prospects later in life, but for what the prospective parents would regard as the 'best child', all things considered. Some of our participants indeed thought that, should information about non-health-related traits come 'for free' as part of a comprehensive test, couples would be interested in including this into the selection process. On the one hand, one participant linked this to the idea of parents putting pressure on their children to perform, which is a far cry from the parental duty to avoid grave suffering in offspring described by Roberts and Franklin. On the other hand, some scholars have argued that selection for non-health-related traits that may be beneficial to the future child should be considered a parental duty, rather than an expression of a parental whim (Savulescu and Kahane, 2009).

Preconception carrier screening and embryo screening for all

Confronted with the scenario of testing for a broader range of genetic disorders, participants argued that to avoid technical problems related to single-cell comprehensive embryo testing, it would be more advisable to preconceptionally test the parents first. If such a preconception test reveals that the couple is at high genetic risk, a targeted test can thereafter be used for the embryo:

> So I think the one privilege that an infertile couple has is that they have the opportunity—they haven't had an affected child, they haven't had a child—, so they can actually ask the question am I carrying anything deleterious? And in particularly you might have an abnormality related to infertility for example, that you can pass on to your children, if you have IVF treatment. So I almost certainly think that patients will be tested, [and] if then you find anything [deleterious] then you will be testing the embryo.

Remarkably in this quote, the participant refers to the possibility 'couples undertaking IVF' have of being genetically tested before conceiving as a 'privilege', in comparison with current PGD couples who often have to find out about genetic defects the hard way, by having an affected child first. This participant firmly believes that in the near

future, all couples visiting the IVF clinic for fertility problems will be tested for carrying at least the most common genetic diseases. Should these tests reveal that they are at risk of transferring a genetic disease, they could then choose to take the PGD route, and opt for targeted genetic testing, possibly combined with comprehensive chromosome screening. It was objected that with this approach, potential *de novo* mutations are not detected. One participant, however, considered the occurrence of *de novo* mutations to be too rare to warrant the use of whole-genome sequencing of the embryo rather than of the parents:

> So in terms of de novo mutations there will be some new mutations that we will miss. So we will never completely eradicate genetic diseases unless we do the complete screening of the embryo. But I just think on a practical level there is so much more to find in the parents than there is in the embryo.

One uncertainty with regard to preconception testing is whether this will be provided via the 'health care system'. Although it was acknowledged that proper genetic counseling is needed both for comprehensive preconception screening and for comprehensive embryo testing, it was assumed that in the future direct-to-consumer genetic testing companies may play an important role:

> And will happen in the very near future I think is what [. . .] said, will we be sending our samples to 23andMe for our premarital screening, and we'll find out everything and then we will decide . . .

In this quote, she suggests that decisions about which reproductive route to take may not be made in the context of an official centre for medical genetics or IVF centre, but may be made by couples beforehand, based on the outcome of privately pursued genetic testing.

Our participants suggested that preconception carrier screening (PCS) 'may be universally offered' to couples visiting the IVF clinic. However, if aneuploidy embryo screening becomes a reliable test, this could be offered to all IVF couples as well. In the following quote, one participant argues that the number of potential patients that may benefit from this technique may increase, and eventually, the technique may be universally applied in the IVF clinic:

> And so I have often argued that if we have a low cost, accurate, comprehensive test for errors at the chromosomal level, that was cheap also. . . . But we don't have that. If we did have that we'd screen every embryo before we put it back. Because of the high level of gross genetic abnormalities in embryos . . .

However, another participant stated that comprehensive screening techniques could be requested by couples that would not be candidates for PGS or PGD at present:

> Because exactly what happens in the future, unfortunately I think they are quite right. It is going to be the wealthy people. . . . I could see a stage coming where we are really doing this, the rich people decide I want the healthiest embryo I am going to go to PGD although I am totally fertile, I am not carrying anything major, but you know we have got tests for diabetes. . . . That is already there, we could test an embryo on diabetes predisposition, BRCA and other inherited cancers, so we could do this now.

In this quote, the participant explicitly worries about the possibility that affluent couples will want their embryos screened for certain susceptibility genes, even if they are fertile or not known carriers of serious diseases. She also states that even at the moment, such tests could be developed and applied.

When considering the options provided by our participants, it became clear that genetic testing in the IVF practice may become primarily an issue of 'smart combinations'. For example, targeted PGD could be supplemented with comprehensive chromosome screening to check for the embryo that is free of the disease and has the most chance of leading to a successful pregnancy. In the context of PGS, aneuploidy screening could be supplemented with screening for Mendelian diseases. A recurrent theme in the expert-panel discussion was the idea of offering PCS to all IVF patients prior to treatment. For example, should PCS of a given couple reveal that this couple is at risk of transmitting a genetic disease to its offspring, targeted PGD could be offered. Such targeted PGD could be accompanied by comprehensive aneuploidy screening to enhance the chance of a successful pregnancy. Alternatively, some couples may wish to skip PCS and opt only for comprehensive embryo screening. In all of these scenarios, the number of conditions screened for in the tests (both of the couples as well as the embryos) may vary from a few conditions simultaneously to the entire genome.

The concept of PCS is not entirely new. It is available mainly in countries with populations affected by a high frequency of specific recessive diseases, such as the program aimed at detecting carriers of thalassemia in Cyprus. Now that technologies for widening the scope of such testing become available, there is a recent trend toward increasing the number of diseases targeted in preconception screening, a possibility that is already marketed to the general population by some commercial companies (Health Council of the Netherlands, 2010; Borry *et al.*, 2011). Our participants saw PCS first and foremost as a solution to technical problems regarding the interpretation of genetic data. However, it may also serve as a means to enhance a couple's reproductive autonomy, as they can now choose from different reproductive options, such as gamete donation or adoption, before undertaking burdensome IVF/PGD treatment (De Wert *et al.*, 2011). Moreover, with comprehensive embryo screening, the genome of an embryo may be sequenced both as a means to allow selection and to provide health information about the child to come. This can have many benefits with regard to prevention and life style recommendations, but also opens up a whole can of ethical worms in need of further scrutiny, and the distinction between testing embryos to make decisions about selection and testing future children becomes blurred (De Wert, 2009). Indeed, many authors defend that genetic testing of minors for late onset diseases is in contradiction to the right of minors (not) to know this information (Borry *et al.*, 2009). PCS and, if necessary, targeted PGD would avoid the issue of children being born whose entire genome is known, as a complete scan of the embryo is not necessary. No doubt PCS also raises its own ethical issues, such as concerns about possible pressure from healthcare professionals, about the further medicalization of procreation and the risk that public health concerns interfere with reproductive autonomy (De Wert *et al.*, 2011). Therefore, further reflection on which combination is the 'smartest' from an ethical point of view is also warranted.

Limitations and Conclusion

We acknowledge that our study has several limitations. First, only PGD scientists and practitioners were part of our expert panel. In

order to achieve a complete view on the challenges posed by the introduction of comprehensive screening, other stakeholders such as IVF and PGD patients, genetic counsellors and fertility doctors should be interviewed. Also, it may be extremely informative to compare the views of medical and scientific professionals in this field with those of sociologists and bioethicists reflecting on these issues. Secondly, the fact that we had only seven participants from four different countries is a severe limitation. However, given the fact that our participants were pioneers in the field of embryo testing and that to our knowledge a study of similar design on the topic of comprehensive embryo testing has not been undertaken before, we believe that this study has value and can be instructive with regard to possible future directions of ethical investigation.

In our expert panel, participants agreed that broadening the scope of embryo testing is a likely development. Such broadening can include PGD combined with aneuploidy screening, or PGS with testing for common Mendelian disorders. In the future, it may also include a whole-genome scan of the embryo. Also, different testing combinations are possible, such as comprehensive PCS followed by targeted embryo testing and aneuploidy screening, or PCS followed by a whole-genome sequencing of the embryos. Ethical reflection on this development should be both anticipatory and realistic. Indeed, the discourse regarding the ethical consequences of the genetic revolution has sometimes focused on futuristic scenarios. Such scenarios include either selecting the best embryo from widely diverse genetic profiles or even altering an embryo's genetic makeup. The possibilities these developments entail to select against different conditions and aberrations and even character traits have been either hailed or condemned. At the same time, there is a need for a focus on real-life scenarios rather than speculations about the future. With the advent of microarrays and whole-genome sequencing in the IVF clinic, the possibility of considering more comprehensively the genome of preimplantation embryos is a development going on as we speak. With PGS, this possibility will not only be limited to couples at high risk of transferring a genetic condition, but to all IVF patients, and even to all couples with a desire to have children. However, as our participants have stressed, selection based on genetic makeup of embryos will, for the time present, still be severely limited by technical and biological factors. Moreover, the reflection on the technique of embryo screening itself should be embedded in a wider reflection on genetic screening at different stages of a subject's life, as our participants' emphasis on PCS has shown.

Our expert panel study has shown that scientists believe an ethical reflection on the issue, which is both informed by these limitations but at the same time not afraid of looking ahead, is called for. An uncertainty, which should be further studied, is the extent to which the possibility to widen selection choices is welcomed or even desired by infertile coupes seeking IVF or by couples with an indication for PGD. As Richard Sharp has argued, studying how patients perceive benefits and risks of multiplexed testing with microarrays may be the best way to prepare for the more complex issues whole-genome screening will introduce. Taking small steps may be the best way to prepare for the huge complexity of data interpretation and counseling whole-genome screening will entail (Sharp, 2011). We believe that this holds true also for embryo testing, as microarrays are now gradually entering the clinical practice.

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Authors' roles

G.M.W. and W.J.D. were moderators of the expert panel. K.H. was an observer. The discussion was transcribed by K.H. A first-pass analysis of the data was made by K.H. using NVIVO9. The analysis was double-checked and fine-tuned by G.M.W., W.J.D., J.P.M.G. and K.H. K.H. wrote the first draft of the manuscript, which was reviewed, supplemented and corrected by G.M.W., W.J.D. and J.P.M.G. All authors reviewed and approved the final version.

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Conflict of interest

The authors declare no conflict of interest.

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